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10/550,410	06/23/2006	James Peter Burnie	87278.2740	2177

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
08/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@bakerlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,410	BURNIE ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13,18-23,26,28,29 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6,13 and 23* is/are allowed.

6)☒ Claim(s) *1-3, 10,18-22, 26, 28, and 29* is/are rejected.

7)☐ Claim(s) *4,5 and 7-9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed 4-8-10. Claims 1, 3, 5, 7-9, 18-19, 21-23 have been amended. Claims 1-10, 13, 18-23, 26, and 28-29 and 53 are pending and under examination.

Objections/Rejections Withdrawn

2. In view of the Applicant's amendments and remarks the following objections/rejections are withdrawn.

a) Rejection to claim 1 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in light of applicant's amendment thereto.

b) Rejection to claim 5 under 35 U.S.C. 112, first paragraph, drawn to a host cell is withdrawn in light of applicant's amendment thereto.

c) Rejection of claims 18 and 22 reciting the limitation " fragment thereof " under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

d) Rejection of claims 19 and 21 reciting the limitation "composition" under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

e) Rejection of claim 23 reciting the limitation "medicament" under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

f) Rejection of claims 5 and 7-9 reciting the limitation "the vector" under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

g) Rejection of claim 21 reciting the limitation "fragment" under 35 U.S.C. 112, second paragraph is withdrawn in light of applicant's amendment thereto.

h) Rejection of claims 18 and 20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

3. The rejection of claims 19, 22, and 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, April 8, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants state claims 19 and 22 have been amended so that they now relate to a polypeptide with the sequence of SEQ ID NO: 2 (i.e., 100% sequence identity) or an antibody thereto. Applicant's state claim 19 also refers to "an isolated antigenic fragment of a polypeptide consistent with SEQ ID NO: 2". Applicants argue SEQ ID NO: 2 is disclosed in the specification and therefore no additional or different amino acids are required in order to generate antigenic fragments of the polypeptide of SEQ ID NO: 2.

Examiners Response to Applicants Arguments:

With regard to Point (A), Claim 19 has been amended to a method for detecting the presence of an isolated antibody or an antigen binding fragment that binds specifically to *Clostridium difficile* lactate dehydrogenase in a sample, the method comprising the steps of: i) contacting the sample with the composition of claim 1 an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or an isolated antigenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2; ii) detecting any antibody-antigen binding reaction; and iii) correlating the results of detection step (ii) with the presence of isolated antibody specific against *Clostridium difficile* lactate dehydrogenase in the sample. However, the claims encompass antigenic fragments of SEQ ID NO: 2 in the method for detecting the presence of an antibody or an antigen binding fragment that binds specifically to *Clostridium difficile* lactate dehydrogenase. Claim 22 has been amended and encompasses antibodies or an antigen-binding fragment thereof in the method for treating *Clostridium difficile* infection in a patient.

The specification discloses experiments using fractionated *Clostridium difficile* protein extracts and antisera obtained from patients infected with C. difficile which detected C. difficile protein (SEQ ID NO: 2), which is 36Kda lactate dehydrogenase (LDH) (see pg. 13 lines 1-10 and pgs. 14-24). The specification discloses the LDH (SEQ ID NO: 2) is immunoreactive and is recognized by antibodies within sera (see pgs. 21-24). Hence, the specification discloses the polypeptide comprising SEQ ID NO: 2 and SEQ ID NO: 1, a nucleic acid that encodes the polypeptide comprising SEQ ID NO: 2, which have specific biological properties dictated by the structure of the protein and the corresponding structure of the structural nucleotide sequence which encodes it. Therefore a nexus between the structure of a protein (SEQ ID NO: 2) and a nucleotide sequence (SEQ ID NO: 1) and the structure of the protein encoded, and the function of that encoded protein, meet the written description provision of 35 USC 112, first paragraph. Hence, the specification is silent with regard to antibodies raised against antigenic fragments (polypeptides) of SEQ ID NO: 2, wherein said polypeptides must bind to antibodies against wild-type *Clostridium difficile* lactate dehydrogenase. Moreover, the specification is silent with regard to the immunoepitopes of variants of SEQ ID NO:2 that must be present in a sample that convey the ability of binding to antibodies and the immunoepitopes of variants of SEQ ID NO:2 capable of therapeutic efficacy for treating *Clostridium difficile* infection in a patient, so that one of skill in the art which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Moreover, the claims are directed toward to variants having different possibilities of changes to the amino acid sequence of SEQ ID NO: 2 in the recited method. Even though one could screen for which changes in SEQ ID NO: 2 possibly retain binding, the courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus or how to identify their common structural features. Therefore the genus is not representative of the claimed invention, thus specification does not provide a correlation between the structures of the claimed variant polypeptides with regards to the functions set forth in the recited claim.

As outlined previously, the claims are drawn to methods of detecting antibodies raised against variant polypeptides (antigen-binding fragments thereof) that bind to *Clostridium difficile*

lactate dehydrogenase utilizing said variant polypeptides (antigenic fragments) of SEQ ID NO:2 and furthermore for treating *Clostridium difficile* infection in a patient utilizing variant polypeptides (antigen-binding fragments thereof).

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention.

The claims are drawn to a vast genus of antibodies raised against variant polypeptides (antigen-binding fragments thereof) that bind to *Clostridium difficile* lactate dehydrogenase utilizing said variant polypeptides (antigenic fragments) of SEQ ID NO:2 and furthermore for treating *Clostridium difficile* infection in a patient utilizing variant polypeptides (antigen-binding fragments thereof), wherein said variant polypeptides must bind to antibodies against wild-type *Clostridium difficile* lactate dehydrogenase. Therefore to adequately describe the claimed genus of polypeptides, applicants must adequately describe which portion of antigenic determinants (immunoepitopes) convey the ability to bind to antibodies against wild-type *Clostridium difficile* lactate dehydrogenase and are required to induce antibodies that would bind to wild-type *Clostridium difficile* lactate dehydrogenase. Also Applicant must adequately describe immunoepitopes capable of therapeutic efficacy for treating *Clostridium difficile* infection in a patient.

The specification discloses experiments using fractionated *Clostridium difficile* protein extracts and antisera obtained from patients infected with C. difficile which detected C. difficile protein (SEQ ID NO: 2), which is 36Kda lactate dehydrogenase (LDH) (see pg. 13 lines 1-10 and pgs. 14-24). The specification discloses the LDH (SEQ ID NO: 2) is immunoreactive and is recognized by antibodies within sera (see pgs. 21-24). The specification discloses the polypeptide comprising SEQ ID NO: 2 and SEQ ID NO: 1, a nucleic acid that encodes the polypeptide comprising SEQ ID NO: 2(a polypeptide with defined structure and function). Consequently, SEQ ID NO:1 and SEQ ID NO:2 meet the written description provision of 35

USC 112,first paragraph. Hence, the specification discloses the polypeptide comprising SEQ ID NO: 2 and SEQ ID NO: 1, a nucleic acid that encodes the polypeptide comprising SEQ ID NO: 2, which have specific biological properties dictated by the structure of the protein and the corresponding structure of the structural nucleotide sequence which encodes it. Therefore a nexus between the structure of a protein (SEQ ID NO: 2) and a nucleotide sequence (SEQ ID NO: 1) and the structure of the protein encoded, and the function of that encoded protein. However, said data indicated does not provide a correlation between the structure of the claimed polypeptide and the functions set forth in the instant claims. Furthermore Applicants have not disclosed variants of the above genus, capable of treating a *Clostridium difficile* infection.

Moreover, the specification, does not disclose distinguishing and identifying features of a representative number of members of the genus of variant polypeptides (immunoepitopes) of SEQ ID NO:2, to which the claims are drawn, such as a correlation between the structure of immunoepitope for the genus of a variant polypeptides (immunoepitopes) of SEQ ID NO: 2 and its recited functions aforementioned above.

Hence, the specification is silent with regard to antibodies raised against antigenic fragments (polypeptides) of SEQ ID NO: 2, wherein said polypeptides must bind to antibodies against wild-type *Clostridium difficile* lactate dehydrogenase. Moreover, the specification is silent with regard to the immunoepitopes of variants of SEQ ID NO:2 that must be present in a sample that convey the ability of binding to antibodies and the immunoepitopes of variants of SEQ ID NO:2 required to induce antibodies that would bind to wild-type *Clostridium difficile* lactate dehydrogenase. Also the specification is silent with regard to the immunoepitopes of variants of SEQ ID NO:2 capable of therapeutic efficacy for treating *Clostridium difficile* infection in a patient, so that one of skill in the art which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Moreover, the claims are directed toward to variants having different possibilities of changes to the amino acid sequence of SEQ ID NO: 2 in the recited method. Even though one could screen for which changes in SEQ ID NO: 2 possibly retain binding, the courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus or how to

identify their common structural features. Therefore the genus is not representative of the claimed invention, thus specification does not provide a correlation between the structures of the claimed variant polypeptides with regards to the functions set forth in the recited claim.

For example, given a substitution mutant of SEQ ID NO: 2, there are 62 possibilities of SEQ ID NO: 2 (20% of SEQ ID NO:2). For example, given a single substitution mutant of SEQ ID NO: 2, for every single amino acid modified by substitution, there are a total of 19 possibilities for a single amino acid substitution as claimed in claims 19, 22, and 26. Moreover, given the instant claims encompass multiple substitution mutants, deletion mutants, and or insertional mutants, the total number of variants encompassed by the instant claims are incalculable. Moreover, with the exception of an isolated polypeptide comprising SEQ ID NO:2 and an isolated nucleic acid molecule of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision all the contemplated variants and binding fragments because the genus is so highly variant and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Therefore, the specification provides insufficient written description to support the genus of variant polypeptides (immunoepitopes) of SEQ ID NO:2 in the recited methods encompassed by the claims.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Furthermore the specification lacks written description of the instant antibody or antigen fragment thereof that

specifically binds to variants. For example, Colman et al. (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that a single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect in antibody binding. This underlies the importance of the description of the immunoepitopes that are protective and which conservative amino acid substitutions and where and how many changes can the immunoepitopes tolerate and still retain the ability to protect from infection.

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of variant polypeptides (immunoepitopes) of SEQ ID NO:2, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of variant polypeptides (immunoepitopes) of SEQ ID NO:2, with the recited activities. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of variant polypeptides in the claimed invention possessing the functional limitations is not deemed representative of the genus of variant polypeptides to which the claims refer and therefore the claimed invention is not properly disclosed.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1 and 28 under 35 U.S.C. 102(b) as being anticipated by (Cerquetti et al 1992 Microbial Pathogenesis Vol. 13 pgs. 271-279 as evidenced by Wright et al 2005 Proteomics Vol. 5 pgs. 2443-2452) are maintained for the reasons set forth in the previous office action.

Applicants arguments filed in response to the 35 U.S.C. 102(b), April 8, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants argue Cerquetti refer to a "36 kDa antigen" that was not categorically established. Applicants state Cerquetti disclose in the paragraphs in pages 273 and 274 that the carbohydrate accounted for 9% of the purified protein on a weight base" thus indicating that the protein component of 36 kDa antigen was actually significantly less than 36 kDa. The subsequent test to confirm these results (see page 274, first paragraph of Cerquetti) failed so the molecular weight of the protein component of the antigen was not conclusively established. Applicants state it is consistent with at least some of the results from Cerquetti that the protein components of the antigen had a molecular weight of around 32.8 kDa (i.e., 36 kDa - 9% by weight). Applicants argue that the reference of Wright will reveal, there are, in fact, several other proteins which have a molecular weight consistent with the antigen reported by Cerquetti, aside from lactate dehydrogenase (see Table 2). Applicants argue that since the molecular weight of the antigen in Cerquetti was only estimated by SDS- PAGE, it would not be unreasonable to conclude that the antigen could have been a C. difficile protein having a theoretical molecular mass slightly above or below 36 kDa, of several other proteins with similar molecular weights in Wright.

Examiners Response to Applicants Arguments:

With regard to Point (A), Applicants response that several other proteins would have a molecular weight consistent with the antigen reported by Cerquetti et al, aside from lactate dehydrogenase is unpersuasive because Cerquetti et al teach a 36 kDa immunodominant antigen of *Clostridium difficile*. Furthermore, Cerquetti et al confirm the 36 kDa immunodominant antigen of *Clostridium difficile* by immunoblotting the 36kDa antigen of Clostridium difficile with monospecific rabbit antiserum (see pg. 274 Figure 4). Furthermore, Wright et al disclose a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36kDa (see pg. 2450 Table 2) which is consistent with the antigen reported by Cerquetti. Therefore said 36 kDa immunodominant antigen of *Clostridium difficile* is deemed, in the absence of evidence to the contrary, to be the same as the *Clostridium difficile* lactate dehydrogenase recited in the instant claims as evidenced by Wright et al. Consequently, the *Clostridium difficile* lactate

dehydrogenase disclosed by Cerquetti et al as evidenced by Wright et al and the *Clostridium difficile* lactate dehydrogenase of the instant claims would have the same chemical, biological and immunological properties. Moreover, although the reference Cerquetti et al does not disclose the *Clostridium difficile* lactate dehydrogenase as having a specific molecular weight, the mere discovery of the molecular weight imparts no novelty to the protein. Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel difference between the claimed product (*Clostridium difficile* lactate dehydrogenase) and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Therefore the rejection is maintained.

As outlined previously, the claims are drawn to a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO:2 (claim 1), a composition comprising the amino acid sequence of SEQ ID NO:2 (claim 28).

Cerquetti et al teach a 36 kDa immunodominant antigen of *Clostridium difficile*. The specification teaches SEQ ID NO: 2 encodes a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36 kD, wherein a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36 kD is also referenced in Wright et al. (see pg. 2450 Table 2). Therefore, it is deemed, in absence of evidence to the contrary that the 36 kDa polypeptide of Cerquetti et al. is the same as the polypeptide of SEQ ID NO:2 of the instant invention. Therefore given the polypeptide of the instant invention and 36 kDa immunodominant antigen of Cerquetti et al are deemed to be the same and the sequence of a polypeptide is an inherent feature of a polypeptide both polypeptides would necessarily have the same amino acid sequence. Moreover, although the reference Cerquetti et al does not disclose the *Clostridium difficile* lactate dehydrogenase as having a specific molecular weight, the mere discovery of the molecular weight imparts no novelty to the protein. Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel or unobvious difference between the claimed product (*Clostridium difficile* lactate dehydrogenase) and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Therefore the

polypeptide of Cerquetti et al anticipates a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2 and a composition comprising said polypeptide.

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1-3, 10, 21, and 28-29 under 35 U.S.C. 103(a) as being unpatentable over (Cerquetti et al 1992 Microbial Pathogenesis Vol. 13 pgs. 271-279) and (Campbell Chapter 1 pg. 1 Monoclonal antibody Technology pgs. 3-5, 1984) as evidenced by (Wright et al 2005 Proteomics Vol. 5 pgs. 2443-2452) is maintained for the reasons set forth in the previous office action.

Applicants arguments filed in response to the 35 U.S.C. 103(a), April 8, 2010 is carefully considered, but not found to be persuasive for the reasons below. **Applicant argues**:

A) Applicants argue Cerquetti refer to a "36 kDa antigen" that was not categorically established. Applicants state Cerquetti disclose in the paragraphs in pages 273 and 274 that the carbohydrate accounted for 9% of the purified protein on a weight base" thus indicating that the protein component of 36 kDa antigen was actually significantly less than 36 kDa. The subsequent test to confirm these results (see page 274, first paragraph of Cerquetti) failed so the molecular weight of the protein component of the antigen was not conclusively established. Applicants state it is consistent with at least some of the results from Cerquetti that the protein components of the antigen had a molecular weight of around 32.8 kDa (i.e., 36 kDa - 9% by weight). Applicants argue that the reference of Wright will reveal, there are, in fact, several other

proteins which have a molecular weight consistent with the antigen reported by Cerquetti, aside from lactate dehydrogenase (see Table 2). Applicants argue that since the molecular weight of the antigen in Cerquetti was only estimated by SDS- PAGE, it would not be unreasonable to conclude that the antigen could have been a C. difficile protein having a theoretical molecular mass slightly above or below 36 kDa, of several other proteins with similar molecular weights in Wright. Applicants argue the reference to Wright actually teaches away from the conclusion that the 36 kDa antigen of Cerquetti was C. difficile lactate dehydrogenase and is therefore precluded from use as a reference. See M.P.E.P. 2145(D)(2). Applicants argue a review of these passages in Campbell provides no suggestion or teaching that one would generate antibodies to isolate a gene. Therefore, even if it could be accepted that Cerquetti disclosed the lactate dehydrogenase protein of SEQ ID NO: 2 of the present application, this in no way establishes that it would be obvious to isolate antibodies to isolate the gene encoding the polypeptide. It is notable that Cerquetti does not disclose the function or amino acid sequence of the protein component of the 36 kDa antigen. Applicants argue it is not seen that there is any teaching in Campbell that would teach a skilled person to obtain the nucleic acid sequence from an antigen, under such circumstances.

Examiners Response to Applicants Arguments:

With regard to Point (A), Applicants response that several other proteins would have a molecular weight consistent with the antigen reported by Cerquetti et al, aside from lactate dehydrogenase is unpersuasive because Cerquetti et al teach a 36 kDa immunodominant antigen of *Clostridium difficile*. Furthermore, Cerquetti et al confirm the 36 kDa immunodominant antigen of *Clostridium difficile* by immunoblotting the 36kDa antigen of Clostridium difficile with monospecific rabbit antiserum (see pg. 274 Figure 4). Furthermore, Wright et al disclose a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36kDa (see pg. 2450 Table 2) which is consistent with the antigen reported by Cerquetti. Therefore said 36 kDa immunodominant antigen of *Clostridium difficile* is deemed, in the absence of evidence to the contrary, to be the same as the *Clostridium difficile* lactate dehydrogenase recited in the instant claims as evidenced by Wright et al. Consequently, the *Clostridium difficile* lactate dehydrogenase disclosed by Cerquetti et al as evidenced by Wright et al and the *Clostridium difficile* lactate dehydrogenase of the instant claims would have the same chemical, biological

and immunological properties and which inherently have the characteristics of a fragment of the instant invention. Moreover, although the reference Cerquetti et al does not disclose the *Clostridium difficile* lactate dehydrogenase as having a specific molecular weight, the mere discovery of the molecular weight imparts neither nor novelty or obviousness to the protein. Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel or unobvious difference between the claimed product (*Clostridium difficile* lactate dehydrogenase) and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Therefore the rejection is maintained.

With regard to Campbell, Examiner disagrees with Applicants response that Campbell provides no suggestion or teaching that one would generate antibodies to isolate a gene. Campbell teach when a protein has been identified one would want to generate antibodies to isolate a gene (see pg. 23 column 2 pg. 24 column 1). Therefore, given that Cerquetti et al necessarily teach a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2 and a composition comprising said polypeptide and given that Campbell teach when a protein has been identified one would want to generate antibodies to isolate a gene indicating the teachings of Cerquetti et al and Campbell are known in the art, thus leading to predictable results it would be obvious to combine the teachings without an express statement of motivation to make an isolated antibody or antigen-binding fragment thereof that binds specifically to the polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2, to make an isolated nucleic acid molecule encoding the polypeptide, wherein the isolated nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 1 in a composition or diagnostic kit (as kit is defined as a collection of items). KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**). Therefore the rejection has been maintained.

As outlined previously, the claims are drawn to a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO:2 (claim 1), an isolated nucleic acid molecule

encoding the polypeptide (claim 2), wherein the isolated nucleic acid comprises the nucleic acid of SEQ ID NO: 1 (claim 3), an isolated antibody or antigen binding fragment thereof binds specifically to the polypeptide, a diagnostic test kit, comprising one or more of: the isolated antibody or fragment, or the composition, or both; and instructions for use (claim 21), a composition comprising the amino acid sequence of SEQ ID NO:2 (claim 28), an isolated nucleic acid molecule, comprising a nucleic acid molecule sequence at least 80% identical to SEQ ID NO:1 (claim 29).

Cerquetti et al teach a 36 kDa immunodominant antigen of *Clostridium difficile* (see title and abstract). The specification teaches SEQ ID NO: 2 encodes a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36 kD, wherein a *Clostridium difficile* lactate dehydrogenase with a molecular weight of 36 kD is also referenced in Wright et al. (see pg. 2450 Table 2). Therefore, it is deemed, in absence of evidence to the contrary that the 36 kDa polypeptide of Cerquetti et al. is the same as the polypeptide of SEQ ID NO:2 of the instant invention. Therefore given the polypeptide of the instant invention and 36 kDa immunodominant antigen of Cerquetti et al are deemed to be the same and the sequence of a polypeptide is an inherent feature of a polypeptide both polypeptides would necessarily have the same amino acid sequence. Moreover, although the reference Cerquetti et al does not disclose the *Clostridium difficile* lactate dehydrogenase as having a specific molecular weight, the mere discovery of the molecular weight imparts no novelty to the protein. Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel or unobvious difference between the claimed product (*Clostridium difficile* lactate dehydrogenase) and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Therefore the polypeptide of Cerquetti et al necessarily teaches a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2 and a composition comprising said polypeptide.

Cerquetti et al does not teach an isolated nucleic acid molecule encoding the polypeptide, wherein the isolated nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 1, an isolated antibody or antigen-binding fragment thereof that binds specifically to the polypeptide, a diagnostic test kit, comprising one or more of: of the isolated antibody or fragment, or the

composition of a polypeptide comprising an amino acid sequence of at least 80% identical to SEQ ID NO:2, or both; and instructions for use, an isolated nucleic acid molecule, comprising a nucleic acid sequence at least 80% identical to SEQ ID NO: 1.

Campbell teaches when a protein has been identified one would want to generate antibodies and to isolate the gene encoding said protein (see pg. 23 column 2 pg. 24 column 1).

Therefore, given that Cerquetti et al necessarily teach a polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2 and a composition comprising said polypeptide and given that Campbell teach when a protein has been identified one would want to generate antibodies to isolate a gene indicating the teachings of Cerquetti et al and Campbell are known in the art, thus leading to predictable results it would be obvious to combine the teachings without an express statement of motivation to make an isolated antibody or antigen-binding fragment thereof that binds specifically to the polypeptide comprising an amino acid sequence at least 80% identical to SEQ ID NO: 2, to make an isolated nucleic acid molecule encoding the polypeptide, wherein the isolated nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 1 in a composition or diagnostic kit (as kit is defined as a collection of items).
KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

New Grounds of Objections

6. Claims 4-5 and 7-9 are objected to as being dependent upon a rejected base claim.

Conclusion

7. No claims are allowed.

Claims 4-5 and 7-9 are objected as being dependent from a rejected base claim.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply

is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert A. Zeman/
for Nina Archie,
Examiner of Art Unit 1645

Nina A Archie
Examiner
GAU 1645
REM 3B31